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EXAMINER	
MERTZ, PREMA MARIA	
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1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,874	SEEGERT ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *8-11 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I (claims 1-7 and 12) in the reply filed 4/25/08 is acknowledged. The traversal is on the ground(s) that the Examiner has made a restriction between Groups I and III-XVI and claim 13 has been amended to recite a method of using the claimed polypeptide-dimer of Group I. Applicants assert that no undue burden would be placed on the Examiner if all the Groups were to be considered in the same application as the searches would be co-extensive. However, the Examiner can only rejoin the groups if the product of Group I is found allowable and if the process of use claims are of the same scope as the allowable product claims.

The requirement is still deemed proper and is therefore made FINAL.

Furthermore, Applicants request rejoinder of the subject matter of Groups III-XVI and elected Group I (see In re Ochiai (37 USPQ2d 1127 (Fed. Cir. 1995)), in which a new, unobvious material is used in a known process. Ochiai determined that a process was free of the prior art if it employed a product which was free of the prior art. However, only if the product claims of Group I are found allowable, the subject matter of Groups II-XVI will be rejoined with the product claims of Group I, if the process claims are of the same scope as the allowable product claims.

Claims 8-11, 13, are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claim Rejections - 35 USC § 112, first paragraph, written description

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2a. Claims 1-7, 12, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth a polypeptide-dimer comprising two soluble gp130 molecules, each of the said soluble gp130 molecules comprising the amino acid sequence SEQ ID NO:2 and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims drawn to mutants or fragments of the extracellular domains D1-D3 of gp130 as recited in claim 1.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or

simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore only an isolated a polypeptide-dimer comprising two soluble gp130 molecules, each of the said soluble gp130 molecules comprising the amino acid sequence SEQ ID NO:2 and equivalent degenerative codon sequences thereof, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. As a result, it does not appear that the inventors were in possession of mutants of the polypeptide-dimer as recited claim 1.

Claim Rejections - 35 USC § 112, first paragraph, scope of enablement

2b. Claims 1-7, 12, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide-dimer comprising two soluble gp130 molecules, each of the said soluble gp130 molecules comprising the amino acid sequence SEQ ID NO:2, and wherein at least one of said soluble gp130 molecules is covalently linked to PEG, does not reasonably provide enablement for a polypeptide-dimer as recited in claim 1 comprising two soluble gp130 molecules, and wherein at least one of said soluble gpl30 molecules is covalently linked to polyethylene glycol and wherein each of said soluble gp 130 molecules consists of the extracellular domains D l-D3 of gp 130 or mutants or fragments thereof that maintain the ability to inhibit the activity of the agonistic complex IL-6-sIL-6R. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1, is overly broad in the recitation of "mutants thereof" since no guidance is provided as to which of the myriad of polypeptide mutants of gp130 encompassed by the claim will retain the desired characteristics. Furthermore, Applicants have failed to disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of gp130. Moreover, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mikayama et al. (1993) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page

10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a gp130 polypeptide other than that exemplified in the specification. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant

specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

With respect to claim 1, and its dependent claims 2-7, 12, the specification is not enabling for "a fragment thereof ", since no reasonable expectation of success and no working example of biologically active fragments of the protein comprising the amino acid sequence shown in SEQ ID NO:2 have been provided in the specification such that fragments of the protein or substitution, deletion, or addition of a single amino acid residue would enable a protein of the biological characteristics of the desired protein. In the instant situation, where the amount of embodiments are innumerable, the enabled embodiment amounts to only one, the complete amino acid sequence of SEQ ID NO:2. It is also asserted that if applicants were to randomly begin making fragments, the success rate, i.e. those which would have biological activity, would be low. There is little to no guidance as to which of these fragments would possess biological activity. Further, if the biological activity belongs to the fragment of the amino acid sequence of SEQ ID NO:2, the specification does not teach either which portion or which amino acids of the sequence are necessary for activity. Additionally, one would expect that fragmentation of a 326 amino acid protein would abolish activity because activity is determined not only by primary sequence, but also three-dimensional structure, as for example, is the case for the ligand binding site of a receptor or for the catalytic site of an enzyme. For these reasons, it would require undue experimentation to determine if the fragment has biological activity, and therefore, to make and use the claimed invention the experimentation would be undue.

Claims 2-7, 12, are rejected under 35 U.S.C. 112, first paragraph insofar as they depend upon the above rejected claim for their limitations.

Claim rejections-35 U.S.C. 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-7, and 12, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as vague and indefinite for several reasons.

Claim 1, line 4, is vague and indefinite because it recites "fragments" which encompasses a single amino acid or a dipeptide. The metes and bounds of this term are unclear.

Claim 1, line 5, is vague and indefinite because it recites "Il-6/sIL-6R" rather than the correct "IL-6/sIL-6R".

Claim 12, is vague and indefinite because it fails to recite "polypeptide-dimer" for consistency. Furthermore, the claim fails to recite that the pharmaceutical composition comprises the "polypeptide-dimer" in a pharmaceutically acceptable carrier.

Claims 6-7 are rejected as vague and indefinite insofar as they depend on the above rejected claim 1 for their limitations.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4a. Claims 1-5, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 1148065 A1 (2001).

The reference teaches a polypeptide-dimer and a pharmaceutical composition thereof comprising two soluble gpl30 molecules, wherein at least one of said soluble gpl30 molecules is covalently linked to polyethylene glycol and wherein each of said soluble gp 130 molecules consists of the extracellular domains Dl-D3 of gp 130 or mutants or fragments (see abstract; page 2, column 2, [0013]-[0014]; page 5, column 2, [0038]; column 12, [0054]). The reference teaches that the soluble gp130 molecules are covalently linked to PEG (column 7, [0038]) meeting the limitations of claim 2. The reference also teaches that the gp130 molecules are linked by one or more disulfide bridges (column 2, [0013]) meeting the limitations of claim 5. Therefore, the polypeptide-dimer disclosed in the reference meets the limitations of claims 1-5, 12, of the instant invention.

The polypeptide of the reference also possesses the biological activity as the claimed polypeptide of the instant invention. Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the

claimed subject matter may be an inherent characteristic of the prior art, it has the authority to require the applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP. 2112.01.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5a. Claims 1-6, 12, are rejected under 35 U.S.C. 103(a) as unpatentable over EP 1148065 A1 (2001) in view of Patton et al (U.S. Patent No. 6,838,076).

The disclosure of EP 1148065 A1 (2001) has been set forth above (see paragraph 4a). However, the reference does not teach that in the polypeptide-dimer the two soluble gpl30 molecules are linked to each other through a forked polyethylene glycol.

Patton et al. teaches conjugates of insulin covalently linked to PEG, wherein the PEG is forked PEG (see columns 41-42, claims 1 and 11). The reference also teaches that forked polymers are advantageous because they provide conjugates having molar ratios of 2:1 or greater of PEG to the protein of interest and such conjugates may be less likely to block the receptor site, while still providing the flexibility in design to protect the protein of interest against enzymatic degradation (column 15, lines 17-61, specifically lines 55-61).

Therefore, at the time the invention was made, it would have been *prima facie* obvious to a person of ordinary skill in the art to modify the soluble gp130 molecules of of EP 1148065 A1 such that it includes linking the molecules to each other through a forked PEG to obtain a polypeptide-dimer comprising two soluble gp130 molecules protected against enzymatic degradation, as taught by Patton et al., to obtain the known functions and advantages of the polypeptide-dimer comprising two soluble gp130 molecules as per the teachings of EP 1148065 A1.

Receptors such as gp130 are well-known in the art as having a short half-life. It would be obvious to modify a short-lived molecule (such as receptors, growth factors or

hormones) with forked PEG to improve the therapeutic potential of the gp130. One would have been motivated to use forked PEG to decrease the gp130 clearance rate *in vivo*. Therefore, it would have been obvious to link the two soluble gp130 molecules through a forked PEG, a long-lived molecule well known in the art as able to increase the stability of rapidly cleared molecules.

4b. Claims 1-5, 7, 12, are rejected under 35 U.S.C. 103(a) as unpatentable over EP 1148065 A1 (2001) in view of Cousens et al (U.S. Patent No. 4,751,180).

The disclosure of EP 1148065 A1 (2001) has been set forth above (see paragraph 4a). However, the reference does not teach that in the polypeptide-dimer the two soluble gpl30 molecules are linked to each other through a flexible peptide linker.

Cousens et al. teaches using a flexible linker "hinge" to separate polypeptides (see column 4, lines 16-47). The reference also teaches that the flexible linker allows for steric flexibility so that the polypeptides would be less likely to interfere with each other, thus preventing incorrect folding (column 15, lines 17-61, specifically lines 55-61).

Therefore, at the time the invention was made, it would have been *prima facie* obvious to a person of ordinary skill in the art to modify the soluble gp130 molecules of of EP 1148065 A1 such that it includes linking the gp130 molecules to each other through a flexible linker to obtain a polypeptide-dimer comprising two soluble gp130 molecules that have steric flexibility, as taught by Cousens et al., to obtain the known functions and advantages of the polypeptide-dimer comprising two soluble gp130 molecules as per the teachings of EP 1148065 A1.

Conclusion

No claim is allowed.

Claims 1-7, and 12, are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Prema Mertz/
Primary Examiner
Art Unit 1646